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Mefloquine pharmacokinetics and resistance in children with acute falciparum malaria

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The pharmacokinetic properties of mefloquine hydrochloride (15 mg base kg^{-1}) were studied in 12 Karen children (five girls, seven boys) aged between 5 and 10 years presenting with uncomplicated falciparum malaria. The drug was well tolerated. Mean (s.d.) peak blood drug concentrations of 2031 (831) ng ml^{-1} were reached in a median of 8 (range 6–24) h. Mean (s.d.) estimates for oral clearance and mean residence time were 0.52 (0.27) ml min^{-1} kg^{-1} and 15.3 (4.7) days, respectively. These values are similar to those reported previously in adults. In one child parasitaemia failed to clear despite whole blood mefloquine concentrations which peaked at 1744 ng ml^{-1}; parasitaemia rose and fever recurred when blood drug concentrations had fallen to 442 ng ml^{-1}. The prevalence of highly mefloquine resistant parasites such as this can be expected to increase under drug pressure in this area.

Keywords mefloquine malaria drug resistance

Introduction

Falciparum malaria is a major cause of childhood morbidity and mortality throughout the rural tropics. In recent years, spreading drug resistance in *P. falciparum* has necessitated development of new antimalarial drugs. Mefloquine, a quinoline-methanol compound, is active against multi-drug resistant strains of *P. falciparum*, and was first introduced for clinical use in Thailand (in combination with sulphadoxine and pyrimethamine) in late 1984 (Karbwang & White, 1990). Single dose therapy with this combination has proved simple, well tolerated, and effective. Elsewhere increasing treatment failure rates with chloroquine and sulphadoxine-pyrimethamine will lead to more widespread use of mefloquine, particularly in children (as children comprise the majority of symptomatic cases in areas of high malaria transmission). The pharmacokinetic properties of mefloquine have been defined in adults with acute malaria (Juma & Ogeto, 1989; Karbwang & White, 1990; Karbwang *et al.*, 1988a,b; Looareesuwan *et al.*, 1987) but not in children. We have conducted a prospective study of the pharmacokinetic properties of mefloquine in 12 children with acute uncomplicated falciparum malaria living on the Thai-Burmese border.

Methods

This investigation was conducted in a large camp for displaced persons of the Karen ethnic minority group situated in a hilly, forested, malaria endemic area on the Thai-Burmese border (Nosten *et al.*, 1987, 1991). Mefloquine (at present combined with sulphadoxine-pyrimethamine) at an approximate dose of 15 mg base kg^{-1} (corresponding to 3 tablets for an adult) is the standard single dose treatment for blood slide confirmed infections with *P. falciparum* in this community. Children with acute falciparum malaria aged between 5 and 10 years were enrolled into the study if their parents or guardians gave fully informed consent to repeated blood sampling, if they had received no previous antimalarial drugs, and if there were no signs or symptoms of severe malaria (World Health Organisation, 1986). Temperatures were controlled by tepid sponging before drug administration. This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University.

Procedures

Falciparum malaria was confirmed by demonstration of asexual forms of the parasite on Field's or Giemsa stained blood slides. A full clinical examination was performed and baseline blood samples were taken. A small (22 or 24G) Teflon cannula was inserted into the antecubital vein and maintained patent with heparin saline. Mefloquine tablets (Lariam: Roche) were given in a dose as close to 15 mg base kg^{-1} as possible. The tablets were crushed, suspended in water, and given

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orally through a syringe so that the exact amount was administered. All children were observed closely for vomiting. Whole blood samples (3 ml) were taken for mefloquine assay at 0, 0.5, 1, 2, 3, 4, 6, 8 h, the cannula was then removed, and further samples were taken at 1, 1.5, 3, 4, 7 and 14 days (a longer period of follow up was not possible). Malaria parasite counts were performed at each of these times. Blood samples were stored at −30° C until analysis.

Mefloquine analysis

Mefloquine in whole blood samples was measured by high performance liquid chromatography as described previously using WR 184806 (± 2.8 bis (trifluoromethyl) 4-[1-hydroxy-3-(*N*-tertbutylamino) propyl] quinoline phosphate) as an internal standard (Karbwang *et al.*, 1988a,b). The assay limit was 20 ng ml^{-1}, and interassay coefficients of variation at concentrations between 100 and 600 ng ml^{-1} were less than 7%.

Pharmacokinetic analysis

Whole blood drug concentration-time data were analysed first by non-compartmental methods. Estimated oral clearance was calculated from the dose divided by the total area under the whole blood drug concentration-time curve. A one compartment model was then fitted to the data using PC NONLIN (Statistical Consultants Ltd) in order to derive an estimate for the apparent absorption rate constant.

Results

Clinical and laboratory findings

Seven boys and five girls were studied. The median age was 7 (range 5–10) years and the median weight was 18 (14–22) kg. All but one of the children were febrile when examined; mean (s.d.) admission axillary temperature was 38.1 (0.5)° C. In seven children the spleen was palpable. The mean (s.d.) haematocrit was 33.7 (4.4)% and the geometric mean parasite count was 18,465 (range 80–435,958) μl^{-1}. There were no other haematological or biochemical abnormalities.

Response to treatment

One child immediately regurgitated an estimated 10% of the dose and another (M6) vomited at 4, 9 and 17 h. There was no other evidence of drug toxicity. The mean (s.d.) time until fever remained below 37.3° C was 29.5 (10.4) h. The mean times to 90% parasite clearance and complete clearance were 22.0 (9.7) and 47.7 (25.8) h, respectively, in the 11 children who responded to treatment.

Treatment failure

Patient No 7, a 5 year old 14 kg male child was admitted with a 2 day history of fever. He was lucid, febrile (37° C) and had a palpable spleen. The peripheral blood film

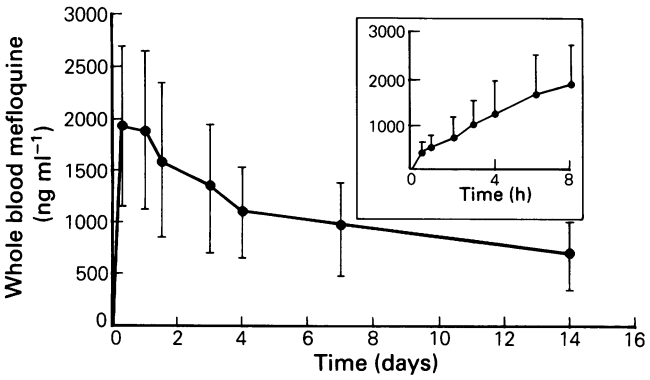

Figure 1 Whole blood mefloquine concentrations (mean ± s.e. mean) following administration of an oral dose of 15 mg kg^{-1} to 12 children with acute uncomplicated falciparum malaria.

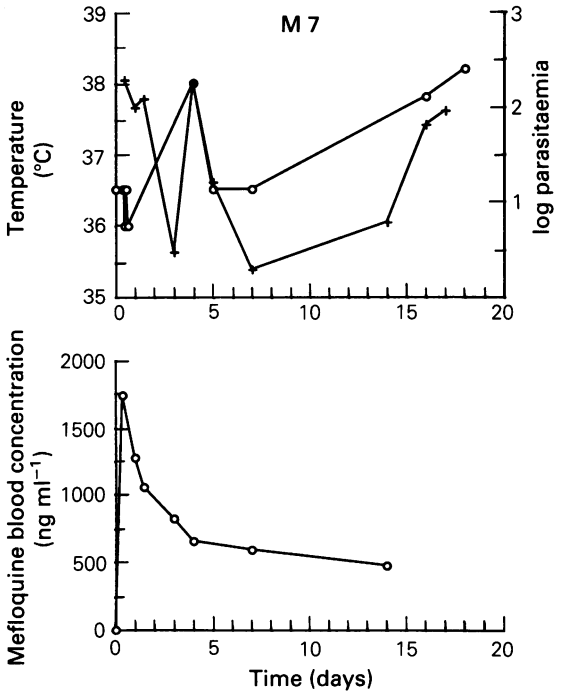

Figure 2 Mefloquine blood concentrations (lower frame), fever (+) and parasitaemia (○) (upper frame) in a child with mefloquine resistant falciparum malaria.

showed a mixed infection with the following parasite counts; *P. falciparum* 6320 μl^{-1} and *P. vivax* 2560 μl^{-1}. Mefloquine (15 mg base kg^{-1}) was administered under supervision as described. The child did not vomit. The subsequent blood drug concentrations and parasitaemia are shown in Figure 2. Fever rose (38° C) and the child was unwell again on the fourth day with a rise in parasite count (181/200 WBC). No further treatment was given at this stage and the following day the child was well again. However, the parasitaemia persisted and on day 16 he was febrile (37.8° C) with parasite counts of 2640 μl^{-1} on D16 and 3560 μl^{-1} on D17. On day 16 he was retreated with mefloquine 20 mg base kg^{-1}. This was well tolerated, the parasitaemia cleared, and he made an uneventful recovery.

Mefloquine pharmacokinetics

Whole blood drug concentrations exceeded 600 ng ml^{-1} by the fourth hour, and were greater than 900 ng ml^{-1} by the sixth hour in all cases (Figure 1). The median (range) time to peak concentration was 8 (6–24) h with a mean (s.d.) peak whole blood drug concentration (C_{max}) of 2031 (831) ng ml^{-1} (range 994 to 3772 ng ml^{-1}). The mean (s.d.) apparent first order absorption half-life was 2.4 (0.6) h. The mean (s.d.) values for oral clearance (CL_{po}) were 0.523 (0.272) ml min^{-1} kg^{-1} with a range of 0.15 to 1.02 ml min^{-1} kg^{-1}. Mean residence times ranged from 9 to 24 days with a mean (s.d.) value of 15 (4) days.

Discussion

Melfloquine absorption in these Karen children with uncomplicated falciparum malaria was comparable with that previously reported in adults. The median time to peak mefloquine concentration was 8 h, and the mean (s.d.) peak mefloquine concentration was 135 (55) ng ml^{-1} mg^{-1} kg^{-1} which compares with ranges of 14–24 h and 112 to 209 (median 144) ng ml^{-1} mg^{-1} kg^{-1} respectively in previous studies in adults (Karbwang & White, 1990; Karbwang *et al.*, 1987, 1988a; Looareesuwan *et al.*, 1987). Mean residence times were also very similar to those reported previously; 15.3 (4.7) days compared with 15.5 (3.1) days in Thai adults with uncomplicated malaria (Karbwang *et al.*, 1988a). As in all previous studies, there was considerable inter-individual variability in the derived pharmacokinetic parameters. Estimates of oral mefloquine clearance have been obtained only three times previously in adults with acute malaria. In the two series from Thailand results were similar; mean values for CL_{po} were 0.62 ml kg^{-1} min^{-1} and 0.57 ml kg^{-1} min^{-1} (Karbwang *et al.*, 1988a,b) and are comparable with the estimates in children in this study; mean (s.d.) CL_{po} 0.52 (0.27) ml kg^{-1} min^{-1}, whereas in African adults with more severe malaria (Juma & Ogeto, 1989) estimates were much higher; mean CL_{po} was 0.89 ml kg^{-1} min^{-1}. This difference is probably related to changes in the fraction of drug absorbed in severely ill patients (Chanthavanich *et al.*, 1985) rather than augmented metabolic clearance.

In this study, one child's infection exhibited high grade resistance to mefloquine (R2 type response). The peripheral parasite count failed to clear following mefloquine treatment with a biphasic recrudescence of parasitaemia. Although the second (day 4) temporary rise in parasite count was associated with symptoms, this could have been a function of the stage and synchronicity of the infection (White & Krishna, 1989) and not necessarily drug resistance, but the second rise in parasitaemia with a return of symptoms on day 16 was unequivocal. Blood mefloquine concentrations had been 472 ng ml^{-1} 36 h previously, and by extrapolation would have been approximately 442 ng ml^{-1} on the day when the child presented with fever and rising parasitaemia. Thus this patient's infecting strain of *P. falciparum* was able to multiply efficiently in the presence of a whole blood concentration of over 400 ng ml^{-1} mefloquine. This *in vivo* documentation of antimalarial drug minimum inhibitory concentration has been determined previously for chloroquine (Hellgren *et al.*, 1989) but not for mefloquine. The impact of highly mefloquine resistant strains of *P. falciparum* on malaria in communities such as this can only increase with the selection pressures of widespread mefloquine administration, and indeed in the last 2 years we have seen a rising number of treatment failures.

The therapeutic ratio of mefloquine in children needs to be defined more precisely, particularly if the incidence of treatment failures continues to rise and dose regimens need to be increased. The relative contributions of drug malabsorption (usually because of early vomiting) and intrinsic parasite resistance will need to be distinguished, although this preliminary study suggests good oral bioavailability in children with uncomplicated malaria.

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